REMARKS

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Upon entry of the above amendments claims 1, 2, 5-9, 11-12 and 27 will be pending. In order to materially advance prosecution and place the application in condition for allowance, the subject matters (or portions thereof) of claims 3, 4 and 10 are incorporated into claim 1.

Therefore, without agreeing with the enablement and written description rejections advanced in the Office Action, it is respectfully submitted that the claims, as amended, fully comply with and satisfy all of the requirements of the first paragraphs of 35 USC 112.

Thus, the present claims are directed to a method of detecting the presence in a sample of body fluid (see, e.g., page 10, lines 1-2) of an exogeneously administered human, bovine or porcine growth hormone and distinguishing the exogeneously administered hormone (polypeptide) from naturally occurring endogenous hormone (polypeptide) present in the body fluid (sample). In this method the sample is subjected to processing, prior to analysis, to enrich or purify the exogeneous hormone, to improve the signal:noise ratio.

Accordingly, when viewed in light of the foregoing amendments, there should be no question but that the specification fully enables one of ordinary skill in the art (which, according to the Examiner is "high, on par with those that hold a Ph.D. in biochemistry") to practice the full scope of the invention. Similarly, there should be no question but that the specification reasonably conveys that Applicants were in possession of the invention being claimed.

In rejecting claims 1-12 and 27, under 35 USC 112, first paragraph, as not being supported by an enabling disclosure, the eight factors summarized in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) were reviewed.

The Quantity of Experimentation Necessary

The conclusion that the quantity of experimentation is high, on the order of several man-years, with little, if any, reasonable expectation of success, is set forth without any factual or evidentiary basis. While it is not agreed that this factor is fairly stated for the previously pending claims, it is far off the mark for the currently pending claims.

Generally, and also with specific regard to the present claims, cloning and expression of tagged polypeptides is essentially a routine task for the person of ordinary skill in the art.

The Amount of Direction or Guidance Provided

The characterization of the amount of guidance as "extremely limited" is believed to be totally inaccurate and without consideration of the level of skill in the art.

Applicant submits that the guidance provided in the specification is rather detailed.

For example, the specification provides clear guidance as to those amino acid residues of a polypeptide which may be substituted, including the factors to be considered in selecting appropriate amino acid residues for substitution (see, e.g., pages 12-13). These details are specifically provided in relation to growth hormone polypeptides, wherein representative specific amino acids are identified as appropriate for substitution. Following the guidelines provided in the specification other substitutions for human, bovine and porcine growth factor could easily be determined without undue experimentation.

The presence or absence of Working Examples

Example 1 shows the construction of an enhanced fluorescent form of hGH. This example also shows how to select the amino acids which are least likely to cause conformational or biological changes of the polypeptide and therefore recommended for substitution.

Example 2 shows the actual genetic technique for making F-W substitutions in hGH.

Example 3 shows fluorescence detection in hGHf.

Example 4 which, while related to calcitonin, demonstrates the differentiation techniques and factors for another polypeptide.

Examples 5-8 provide disclosures for modifying four additional polypeptides, including human growth hormone releasing factor, HGHRF.

Thus, the number of and weight to be accorded the examples supports the conclusion of enablement.

Indeed, the portion of *Genentech v. Novo Nordisk A/S*, 42 USPQ2d 1001, which was emphasized on page 5 of the Action is clearly inapplicable to the present case. This is not a case where "there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out." Nor is this a case where undue experimentation would be required to practice the invention being claimed.

The sentence following the emphasized portion of the quotation from *Genentech* explains that "the knowledge of one skilled in the art" should not be used to supply the novel aspects of the invention. Here, the novel aspects of Applicants' invention are fully and completely elucidated in the specification. Even if other procedures, which are incidental to

the claimed invention, rely on the knowledge of one skilled in the art, such reliance on the level of skill is not contrary to the satisfaction of the enablement provision of Section 112.

Production and Purification of modified hGH protein is described on page 15, starting on line 9.

The Nature of the Invention

While the nature of the invention may relate generally to matters of physiology and chemistry, the invention, more specifically relates to detection of a particular class of hormone, which is well studied in the art, using techniques which are also well established in the art. In view of the considerable research and detailed characterization of human, bovine and porcine growth hormones, there is a considerable high degree of predictability for the enablement requirement.

The citation to Henkin, US 4,066,405 is not believed to be relevant to the issue of enablement. This patent refers to the expression of different polypeptides than those to which the amended claims are concerned and, in any case, does not disclose or relate to mutations or alterations to any particular individual polypeptide sequence.

The State of the Prior Art and the Relative Skill of Those in the Art

As stated previously, the art relating to growth hormones is highly developed and the relative level of skill in the art is correspondingly high.

As evidence relating to the State of the Prior Art and relative level of skill, Applicants will submit the following literature references:

1. Ferrara, P, HGH: Production by genetic engineering for a hormone identical to the natural 22K hormone, Symposium "Quo Vadis?", Sanofi, May 29-30, Toulouse-Labege, France(1985) 147-155.

2. Atkinson T, et al, Human Growth Hormone: Microbial Expression and purification, Biotech, 1 (1985) 1-6.

3. Chang, C N, et al, High-level secretion of human growth hormone by Escherichia coli, Gene, 55 (1987) 189-196.

4. Gray, G L, et al, Pseudomonas Aeruginosa secretes and correctly processes human growth hormone, Biotechnology (1984) 161-165.

5. Franchi, E, et al, A new human growth hormone production process using a recombinant Bacillus subtilis strain, J. Biotechnology, 18 (1991) 41-54.

6. Hsiung, H M, et al, High-level expression, efficient secretion and folding of human growth hormone in Escherichia coli, Biotechnology, 4 (1986) 991-995.

7. Becker, G W, and Hsiung, H M, Expression, secretion and folding of human growth hormone in Escherichia coli, FEBS, 204 (1) (1968) 145-150.

8. Kato, C, et al, Construction of an excretion vector and extracellular production of human growth hormone from Escherichia coli, Gene, 54 (1987) 197-202.

9. Pearlman, R & Bewley, T A, "Stability and Characterisation of Human Growth Hormone," In "Stability and Characterisation of Proteins and Peptide Drugs: Case Histories," (1993) 1-58, eds Y John Wang and Rodney Pearlman. Plenum Press, New York.

10. Smith, C J, et al, Detection and Characterisation of Intermediates in the Folding of Large Proteins by the Use of Genetically Inserted Tryptophan Probes, Biochemistry 30 (4) (1991) 1028-1036.

11. Atkinson, T, et al, High-level microbial expression and purification of recombinant proteins. In "Bioactive Microbial Products 2," (Eds. J D Stowell, P J Bailey and D J Winstanley) (1986) 27-43 Academic Press, London, Winstanley.

A Form PTO-1449 listing each of these articles will be filed with a copy of each document as soon as possible.

In the above literature, the Smith et al article (1991) (co-authored by one of the present inventors) discloses a method for exciting tryptophan fluorescence and measuring same, whether using denatured or native protein.

Chang et al (1987) provides evidence that one skilled in the art would be able to purify growth hormone in a one-step immunoaffinity chromatography step with the resulting protein being of sufficient purity to allow N-terminal sequence analysis. Other purification techniques are also described, e.g., see Pearlman & Bewley (1993).

The Predictability or Unpredictability of the Art

The characterization that the predictability is "quite low" is not only believed to be inaccurate for the previously pending claims but is simply incorrect for the detection of exogenously administered growth hormone as now claimed.

The Breadth of Scope of the Claims

The pending claims are of a scope which is clearly enablement by the specification which provides ample guidance and examples for the practice of the claimed invention.

Accordingly, for all of the foregoing reasons, the rejection for lack of enablement is respectfully traversed.

The rejection for lack of a written description is also respectfully traversed.

In addition to the reasons discussed above with regard to enablement, the Examiner's position is not fully understood. The discussion in paragraph 6 on page 8 appears to be based on the breadth of the previously pending claims rather than on whether the specification reasonably conveyed that Applicants invented the subject matter being claimed.

In any case, in view of the above amendments, this rejection should be withdrawn as the specification provides more than reasonable assurance that Applicants invented the subject matter being claimed.

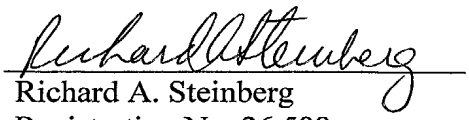
In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue which the Examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Attached is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned **"Version with markings to show changes made"**.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: 

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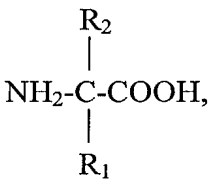
APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

2. (Three times amended) A method of detecting the presence in a sample of a polypeptide exogenously administered to a mammalian subject from whom the sample is obtained, and distinguishing between such an exogenously administered polypeptide and a naturally-occurring endogenous polypeptide present in the sample; the method comprising obtaining a sample of body fluid from the subject; and subjecting the sample to analysis of fluorescence at a suitable wavelength; wherein the sample is subjected to processing, prior to analysis, by one or more of the following: centrifugation; HPLC; FPLC; affinity chromatography; immunoaffinity chromatography; denaturation or heat treatment, so as to enrich or purify the exogenous polypeptide thereby to improve the signal: noise ratio; and wherein the exogenously administered polypeptide has a greater or lesser amount of fluorescence activity, relative to the endogenous polypeptide, at the wavelength(s) analysed, wherein the greater or lesser amount of fluorescence activity is due to the respective presence or absence in the exogenously administered polypeptide, relative to the endogenous polypeptide, of a fluorescent amino acid residue or a synthetic amino acid derivative[,] in the amino acid backbone of the polypeptide, the synthetic amino acid derivative having the formula



wherein R_1 comprises the fluorophone and R_2 is H, OH, halide or substituted or unsubstituted lower alkyl; and wherein the exogenously administered polypeptide comprises human, bovine or porcine growth hormone.

11. (Three times amended) A method according to claim 1, wherein the exogenously administered polypeptide comprises [one of the following: a tagged] human[, bovine or porcine] growth hormone[; tagged calcitonin; tagged erythropoietin; tagged growth hormone releasing factor; tagged insulin; or tagged interleukin-2].

End of Appendix